Breastfeeding and the Risk of Hospitalization for Respiratory Disease in Infancy

A Meta-analysis

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Objective: To examine breastfeeding and the risk of hospitalization for lower respiratory tract disease in healthy full-term infants with access to modern medical care.

Data Sources: MEDLINE, personal communication with researchers, the OVID databases, Dissertation Abstracts Online, and BIOSIS.

Study Selection: The titles, abstracts, and text of studies from developed countries were explored for breastfeeding exposure measures and lower respiratory tract disease hospitalization rates. For summary statistics, we required 3 inclusion criteria: (1) a feeding contrast of a minimum of 2 months of exclusive breastfeeding (no formula supplementation) vs no breastfeeding and (2) study populations that excluded sick, low birth weight or premature infants and (3) reflected affluent regions; 27% of studies met these criteria.

Data Extraction: We abstracted data from all relevant reports.

Data Synthesis: Data from all primary material (33 studies) indicated a protective association between breastfeeding and the risk of respiratory disease hospitalization. Nine studies met all inclusion criteria, and 7 cohort studies were pooled. The feeding contrasts in these 7 studies were 4 or more months of exclusive breastfeeding vs no breastfeeding. The summary relative risk (95% confidence interval) was 0.28 (0.14-0.54), using a random-effects model. This effect remained stable and statistically significant after adjusting for the effects of smoking or socioeconomic status.

Conclusion: Among generally healthy infants in developed nations, more than a tripling in severe respiratory tract illnesses resulting in hospitalizations was noted for infants who were not breastfed compared with those who were exclusively breastfed for 4 months.


Respiratory disease is the leading cause of hospitalization among young children.1 Annually, 6% of infants younger than 1 year are hospitalized for lower respiratory tract diseases (LRTDs), according to trend data (1980-1996) in the United States.2 The costs of these hospitalizations have been conservatively estimated at $300 million, using 1985 dollars.3-5 For decades, severe infantile respiratory illness has been recognized to be an antecedent to childhood asthma.6-8 Recently, respiratory disease severe enough to require hospitalization in infancy has been reported to increase the risk of childhood asthma 10-fold,9 and annual costs for childhood asthma through age 17 years have been estimated to exceed $1.6 billion.10(p790)

Prior reviews of respiratory disease and breastfeeding from developed countries have provided equivocal results.11-14 These studies have used illness episodes as their end point. Because both respiratory illness and infant feeding are manifest on a broad continuum, investigation of this topic is difficult. We chose to focus on hospitalizations for LRTD in infancy as our outcome of interest because it is an important measure of illness severity and is associated with sizable direct and indirect health care costs.

Whereas breastfeeding is widely acknowledged to protect infants in the developing world from acute infectious illnesses, such as gastroenteritis or respiratory disease, the magnitude of its benefit for healthy infants with high standards of living (in terms of medical care and sanitation) is not well delineated. Recommendations from both the Surgeon General and the American Academy of Pediatrics advise women to breastfeed exclusively, that is without formula supplementation, through age 6 months15,16; however, few women follow these recommendations. Whereas 67% of US women initiate breastfeeding, only 31% continue with any breastfeeding at 6 months of age.17,18 The impact of limited breastfeeding on the health of children has not been well studied in developed countries. Evidence-based medicine

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could fill this gap and provide further guidance to women regarding their infant feeding choices.

Our goal for this meta-analysis was to examine the risk of hospitalization for LRTD in healthy full-term infants with access to modern medical care and breastfeeding—which requires definition for both its duration and exclusivity as an infant feeding pattern. In addition, the effects of smoking and socioeconomic status (SES) as possible confounders of the relationship between breastfeeding and hospitalization for LRTD were investigated.

DATA SOURCES

The following eligibility and exclusion criteria were prespecified. Only studies from industrialized nations that reported LRTD hospitalization rates and examined breastfeeding were sought. Studies were ineligible if they focused on geographic regions where gross malnutrition is prevalent or if they focused on children with recognized chronic illnesses (eg, cystic fibrosis), other than allergic conditions. We defined LRTD to include bronchiolitis, asthma, bronchitis, pneumonia, empyema, and infections due to specific agents (eg, respiratory syncytial virus).

A priori, we wished to focus our analysis on studies of healthy full-term infants whose living conditions reflected those of affluent developed nations. We sought studies of populations that excluded sick, premature, and/or low birth weight infants (“sick newborns”). Additionally, we looked for studies that characterized breastfeeding as exclusive (meaning little or no formula offered) and provided a duration of exclusive breastfeeding for 2, 4, or 6 months or total (any) breastfeeding for longer durations. The breastfeeding inclusion criterion was a minimum exposure of 2 months of exclusive breastfeeding or 9 months of total (any) breastfeeding compared with its absence.

We identified 34 relevant research studies through iterative searching methods.20-53 Data were provided without reimbursement from all but one research group, leaving 33 studies with data to examine.53 We searched MEDLINE (National Library of Medicine, Bethesda, Md) for relevant articles published from 1966 to April 11, 2002, and found 2386 citations. The search strategy used was (“respiratory tract diseases”[MeSH] OR “bacterial infections and mycoses”[MeSH] OR “virus diseases”[MeSH] OR “hospitalization[MeSH]” OR “morbidity[MeSH]” AND “breast feeding OR lactation[MeSH]” OR milk, human[MeSH]”: Limits: all infant: birth—23 months. Abstracts for all relevant titles were examined; bibliographies of all articles with useful data, including foreign language publications, were inspected. The OVID system’s databases for evidence-based medicine reviews (EBM Reviews, CCTR, CDSR, DARE, ACP Journal Club, CINAHL, HealthSTAR), Dissertation Abstracts Online, and BIOSIS (for books and conference publications) were searched but provided no additional relevant material. Unpublished data were actively solicited by writing to authors in the field and by contacting members of the International Society for Research in Human Milk and Lactation. Through these combined means, 10 research groups contributed further unpublished data.

DATA EXTRACTION

The investigators independently abstracted the data without blinding using a standardized data-abstraction form. The following information was sought from each paper: authors’ names, title, year of publication, the purpose of the study, the study methods (cohort [prospective or retrospective] or noncohort), the age to which infants were observed, the season in which infants were enrolled, the geographic location of the study, the study size (and the number lost to follow-up), breastfeeding definitions in terms of both its duration and exclusivity, hospitalizations for LRTD, and confounding infant and household factors that studies either controlled for or matched. Data from each study were used to estimate either a relative risk or an odds ratio.

RESULTS

Hospitalization for LRTD, the outcome variable, was prespecified. We excluded reports of pulmonary complications when hospitalization was not required, as well as reports of hospitalizations for upper respiratory tract disease. Whenever possible, we restricted our analysis to first-time hospitalizations for infants within study populations. We did so to avoid any possible distortion from counting repeat hospitalizations of children with chronic conditions not yet diagnosed.

The 33 studies were examined for the inclusion criteria specified above. To make our work generalizable to populations with high standards of living (in terms of medical care and sanitation), we eliminated 7 studies in which this might be disputed: 3 from China,20-22,40 2 from South America,23,43 and 2 from North American Indian populations.23,24 To focus our work on healthy newborn infants, we dropped all studies wherein sick newborns could not be excluded from the study’s data and, applying the inclusion criteria for breastfeeding, we excluded 17 further studies,8 leaving 9 studies.

STUDY SELECTION

Hospitalization for LRTD in infancy was the primary outcome measure. Of the 9 eligible studies, 7 used cohort study designs, allowing us to report summary relative risk ratios. Additionally, the risk difference was calculated for these 7 studies to estimate the number needed to treat to prevent one LRTD hospitalization by exclusive breastfeeding.

The study designs of the 2 remaining studies, a cross-sectional analysis and an ecological design, provided odds ratios. Because of the disparate clinical characteristics of these 2 studies, their data were neither pooled into a separate summary statistic nor included with the cohort data because to do so would have required unjustifiable assumptions.

We computed the summary statistics with 95% confidence intervals using both the random-effects method of DerSimonian and Laird and the fixed-effects method of Mantel and Haenszel.48 We present the results from the random-effects model because this model examines the inference tested in our analysis: would a random sample of studies examining some hypothetical population of studies of breastfeeding and LRTD hospitalization show a significant effect of breastfeeding? This model was preferred because it incorporates both within and between study variance into the point estimate and confidence interval calculations, which usually results in wider confidence intervals. Stata statistical software, version 755 was used for all summary relative risk and odds ratio computations.

STUDY CHARACTERISTICS

Data from 33 studies were examined, and a protective association between breastfeeding and the risk of
LRTD hospitalization was found from each study.20-52 This alone is a remarkably consistent finding for meta-analysis source material.

We present risk ratios, relative risk ratios and odds ratios, for 9 studies; the remaining 24 studies did not meet inclusion criteria, 17 because of design limitations and 7 because of demographic considerations. The Table presents study characteristics for these 9 studies: the exclusion criteria for sick newborns, the length of patient follow-up, and the risk ratio for each study. All 9 reports were published between 1980 and 2001. Four studies were from North America,21,22,33,38 2 were from Australia,36,46 and 1 each was from Scotland,39 New Zealand,34 and Norway.45

**Figure 1.** The risk of hospitalization for lower respiratory tract disease (LRTD) and breastfeeding exposure measures for 7 cohort studies. Breastfeeding diminishes the risk of hospitalization for respiratory disease.

Sizable differences in exposure measures and patient follow-up are noted among the 7 studies summarized. Despite this clinical heterogeneity among these 7 studies, which provide effect estimates that range from 0.12 to 0.65, no evidence of statistical heterogeneity was found when these studies were pooled ($P = .18$). Summary estimates from both the fixed- and random-effects models were similar. The summary risk ratio was 0.28 (0.14-0.54) using the random-effects model.

Additionally, we calculated the number of infants who would need to be breastfed exclusively for 4 or more months to prevent one LRTD hospitalization using the summary risk difference (0.039).56 The number needed to treat was 26.

**SENSITIVITY ANALYSIS**

Because the 7 pooled studies differed clinically with respect to breastfeeding measures, length of follow-up, data collection methods, and, most likely, respiratory disease diagnoses, we performed sensitivity analyses to test the appropriateness of combining these studies. We eliminated each study, one at a time, then the 2 studies with total (any) breastfeeding39,45 (rather than exclusive breastfeeding, because we assumed that to establish a
milk supply, women who breastfed long-term also breastfeed exclusively in the first months) and the 2 studies with retrospective study designs22,38 (rather than prospective study designs). Each time we eliminated 1 or 2 studies, we recalculated the relative risk and its confidence interval. None of these sensitivity analyses resulted in confidence intervals that included the null hypothesis or 1.0. The risk ratios for these sensitivity analyses ranged from 0.25 (0.12-0.52) to 0.47 (0.26-0.84).

To further assess the strength of the summary estimate for this meta-analysis, we examined the magnitude of the risk ratio that would be required from a new, hypothetical study that, when combined with the 7 studies identified here, would produce a summary estimate confidence interval that would include 1.0, or the null hypothesis. We chose a large sample size of 1000 subjects and assumed that half were breastfed—exclusively for 4 or more months—and half were bottle-fed. We then determined that such a hypothetical study would require a risk ratio with a magnitude of 18 or greater simply to call into question the statistical validity of the findings from this meta-analysis.

### SUBGROUP ANALYSES FOR COVARIATES

Smoking and SES are 2 factors that correlate closely with both women’s breastfeeding choices and infant hospitalization.

#### Figure 2. Data stratified on maternal smoking from 3 cohort studies that examine the risk of hospitalization for lower respiratory tract disease (LRTD) and breastfeeding. Breastfeeding exposure measures are presented in Figure 1.

<table>
<thead>
<tr>
<th>Source</th>
<th>Follow-up Period, mo</th>
<th>Hospitalization for LRTD, n/N</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
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<tr>
<td>Beaudry et al²²</td>
<td>6</td>
<td>0/5</td>
<td>0.43</td>
<td>(0.22-0.85)</td>
</tr>
<tr>
<td>Fergusson et al³⁴</td>
<td>24</td>
<td>0/35</td>
<td>0.25</td>
<td>(0.12-0.52)</td>
</tr>
<tr>
<td>Oddy et al⁴⁶</td>
<td>12</td>
<td>7/324</td>
<td>0.47</td>
<td>(0.26-0.84)</td>
</tr>
</tbody>
</table>

#### Figure 3. Data stratified on socioeconomic status from 4 cohort studies that examine the risk of hospitalization for lower respiratory tract disease (LRTD) and breastfeeding. Breastfeeding exposure measures are presented in Figure 1.

<table>
<thead>
<tr>
<th>Source</th>
<th>Low Socioeconomic Status</th>
<th>Hospitalization for LRTD, n/N</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball and Wright²¹</td>
<td>0/49</td>
<td>2/78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaudry et al²²</td>
<td>0/20</td>
<td>22/241</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fergusson et al³⁴</td>
<td>0/25</td>
<td>7/74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oddy et al⁴⁶</td>
<td>22/645</td>
<td>8/178</td>
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<table>
<thead>
<tr>
<th>Source</th>
<th>Mid Socioeconomic Status</th>
<th>Hospitalization for LRTD, n/N</th>
<th>Relative Risk</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Ball and Wright²¹</td>
<td>2/191</td>
<td>0/88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaudry et al²²</td>
<td>0/16</td>
<td>4/87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fergusson et al³⁴</td>
<td>1/106</td>
<td>3/121</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>High Socioeconomic Status</th>
<th>Hospitalization for LRTD, n/N</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball and Wright²¹</td>
<td>0/83</td>
<td>1/9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaudry et al²²</td>
<td>0/13</td>
<td>1/18</td>
<td></td>
<td></td>
</tr>
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<td>Fergusson et al³⁴</td>
<td>0/95</td>
<td>0/31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oddy et al⁴⁶</td>
<td>10/486</td>
<td>2/40</td>
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<td></td>
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</tbody>
</table>

Summary Relative Risk (95% CI) 0.53 (0.30-0.93)
izations. To explore the effects of these covariates on our primary analysis, we present 2 subgroup analyses wherein we adjusted for SES and smoking using stratified methods.

Smoking

Three primary studies provided stratified data on maternal smoking. Figure 2 presents the risks for LRTD hospitalization by breastfeeding exposure and stratified on maternal smoking. The crude risk ratio was 0.19 (0.10-0.38) for these 3 studies; the pooled risk ratio was 0.33 (0.13-0.83) within the smoking strata and 0.58 (0.21-1.59) within the nonsmoking strata. The summary risk ratio adjusting by stratification for smoking was 0.43 (0.22-0.85); no evidence of statistical heterogeneity was found (P = .66). This indicates that smoking does not account for the observed effect of breastfeeding on LRTD hospitalizations.

Socioeconomic Status

Four primary studies provided SES data; 3 provided data stratified on 3 levels of SES, and 1 provided only 2 strata. Two of these studies determined SES by paternal occupation, and 2 determined SES using maternal education. Figure 3 presents the risk data stratified on SES. The crude risk ratio for these 4 studies with SES data was 0.37 (0.15-0.88); the pooled risk ratio was 0.62 (0.30-1.26) within the low SES strata, 0.64 (0.14-2.93) within the mid SES strata, and 0.29 (0.08-1.00) within the high SES strata for these 4 studies. The summary risk ratio after adjusting for SES was 0.53 (0.30-0.93); no evidence of statistical heterogeneity was found (P = .82). This indicates a measurable and independent effect of breastfeeding on the risk of LRTD hospitalization after considering SES.

A remarkably consistent effect was found among all the primary material amassed for this report, which is indicative of a protective role for breastfeeding against common respiratory pathogens. Exclusive breastfeeding for 4 or more months appears to diminish the risk of respiratory hospitalization in infancy to one third or less the risk observed for formula-fed infants, even in developed nations with high standards of living (in terms of medical care and sanitation). The strengths of this analysis include the magnitude of our findings, the search of published and unpublished reports, and attention to 2 important potential confounders, smoking and SES.

The absence of explicit data in the medical literature constitutes a major problem for any study of breastfeeding. This variable requires definition for both its duration and exclusivity; however, in the past, many authors have simplified their consideration of breastfeeding by dichotomizing its exploration. Insufficient data within primary studies made it infeasible to estimate more than one risk level for the effects associated with breastfeeding.

Case-control studies obtained for this review examined some vs no breastfeeding at a given point in time. However, several reports did not distinguish between minimal, partial, or exclusive breastfeeding; thus, feeding contrasts based on imprecisely specified breastfeeding measures did not meet the inclusion criteria for this meta-analysis.

Stringent criteria were applied to the selection of all primary material used to estimate summary statistics. Our summary risk ratios derived exclusively from cohort studies. Because patient exposure data are collected without reference to illness status in cohort studies, recall bias was avoided. Additionally, we summarized only studies that offered a minimum exposure of exclusive breastfeeding for 4 or more months, or at least 9 months of total (any) breastfeeding, compared with no breastfeeding and tested the clinical assumption of combining these exposure measures. Furthermore, because a disproportionate number of sick newborns within a study population could provide a spurious association between breastfeeding and illness, we excluded all studies that included them. Since sick newborns are less able to suckle and, therefore, are more likely to be bottle-fed.

Another challenge to the investigation of protective factors in infancy and respiratory disease is both seasonal and age variation. A 10-fold increase in LRTD hospitalizations occurs during the winter months, and infant respiratory hospitalization rates peak during the first 4 months of life. Therefore, studies examining spring births, when the baseline rate of respiratory disease is normally low, will have fewer outcomes and, thus, less power to detect an association with infant feeding. Publication bias may adversely affect this report but appears unlikely because of our extensive search of both published and unpublished reports (unrestricted to the examination of this study’s hypothesis).

More robust findings appear to cluster with stronger breastfeeding measures (when considering all primary material), consistent with a biological phenomenon. Since maternal milk transmits both immune cells and antibodies to infants, immune modulation could explain the breastfeeding effects that are noted to extend beyond the actual period of exposure. In support of this view, it has been found that lymphocyte profiles differ at 6 months of age between breastfed infants and those who are not breastfed. Moreover, T lymphocyte profiles distinguish children who are prone to asthma in infancy from those not so predisposed. Together, these observations suggest that further elucidation of immune development in relationship to infant feeding practices is warranted.

Alternative explanations for the inverse association between breastfeeding and respiratory disease require consideration. Some observers suggest that maternal smoking may account for the apparent breastfeeding effects because women who smoke are less likely to breastfeed. Others indicate that observed breastfeeding effects are secondary to SES differences among women who do and do not breastfeed. We explored both hypotheses with the available data, and neither was supported. The protective association between breastfeeding and LRTD hospitalizations remained stable and statistically significant after examining the effects of either smoking or SES.

COMMENT

Physician hesitation to separate illness status from breastfeeding exposures and LRTD hospitalizations did not meet the inclusion criteria for this meta-analysis.
Exclusive breastfeeding, that is, breastfeeding without supplementation, for 6 months is currently recommended. Its importance to the prevention of serious health conditions resulting in hospitalization for healthy full-term infants with access to modern medical care, however, has not been well quantified. How much of what type of feeding really makes a difference?

When exclusive breastfeeding is contrasted with lesser levels of breastfeeding, one can begin to measure the sizable health effects associated with this infant feeding pattern. Unless infant feeding patterns are carefully documented, their health effects will not be observed. We report a significant risk reduction in hospitalizations due to respiratory disease for infants who have been exclusively breastfed for 4 or more months.

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